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     (FILE 'HOME' ENTERED AT 16:25:07 ON 20 APR 2002)

     FILE 'REGISTRY' ENTERED AT 16:25:15 ON 20 APR 2002
L1             0 S TCF(W)II/CN
L2             0 S TISSUE(W)CYTOTOXIC(W)FACTOR/CN
L3             0 S TISSUE(W)CYTOTOXIC(W)FACTOR?/CN
L4             0 S TCF/CN
L5             0 S TCF/CN

     FILE 'USPATFULL' ENTERED AT 16:28:53 ON 20 APR 2002
L6            11 S TCF(W)II

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6 ANSWER 1 OF 11 USPATFULL
AN 2002:78210 USPATFULL
TI PREVENTIVE AND/OR THERAPEUTIC AGENT FOR CACHEXIA
IN KOJIRO, MASAMICHI, FUKUOKA, JAPAN
YANO, HIROHISA, FUKUOKA, JAPAN
IEMURA, AKIHIRO, FUKUOKA, JAPAN
PI US 2002041863 A1 20020411
AI US 1999-180586 A1 19990729 (9)
WO 1998-JP999 19980311
PRAI JP 1997-82162 19970314
DT Utility
FS APPLICATION
LREP TESTA HURWITZ & THIBEAULT, PATENT ADMINISTRATOR, HIGH STREET TOWER, 125 HIGH STREET, BOSTON, MA, 02110
CLMN Number of Claims: 2
ECL Exemplary Claim: 1
DRWN 2 Drawing Page(s)
LN.CNT 316
AB The present invention provides an agent for preventing and/or treating cachesia comprising **TCF-II** as an effective ingredient. An excellent agent for preventing and treating cachexia caused by cancer, acquired immunodeficient syndrome (AIDS), cardiac diseases, infectious disease, shock, burn, endotoxinemia, organ inflammation, surgery, diabetes, collagen diseases, radiotherapy, chemotherapy is provided by the present invention and useful for medicine.

L6 ANSWER 3 OF 11 USPATFULL
AN 2001:229197 USPATFULL
TI AGENT FOR PREVENTING AND/OR TREATING MULTIPLE ORGAN FAILURE
IN ARISAWA, HIROHIKO, TOCHIGI, Japan
MASUNAGA, HIROAKI, TOCHIGI, Japan
OGAWA, HIROMI, TOCHIGI, Japan
HIGASHIO, KANJI, SAITAMA, Japan
PI US 2001051146 A1 20011213
AI US 1999-180599 A1 19990827 (9)
WO 1998-JP998 19980311
None PCT 102(e) date
PRAI JP 1997-74372 19970311
JP 1997-157645 19970530
DT Utility
FS APPLICATION
LREP TESTA HURWITZ & THBEAULT, HIGH STREET TOWER, 125 HIGH STREET, BOSTON, MA, 02110
CLMN Number of Claims: 9
ECL Exemplary Claim: 1
DRWN 5 Drawing Page(s)
LN.CNT 527
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention is to provide an agent for preventing and/or treating multiple organ failure comprising Tumor cytotoxic factor-II (**TCF-II**) or Hepatocyte growth factor (HGF) as an effective ingredient.

The agent of the present invention will be useful for preventing and/or treating the development from burn, disseminated intravascular coagulation (DIC), circulatory failure, hemorrhagic shock, infectious disease, acute pancreatitis, ischemic disorder, hepatorenal syndrome, gastrointestinal hemorrhage, nutritional metabolic failure, terminal cancer, acquired immunodeficiency syndrome (AIDS), deterioration of systemic conditions due to radiation affection and cachexia etc. to multiple organ failure.

13500787 BIOSIS NO.: 200200129608
Active site inhibited factor VIIa (ASIS, FFR-rFVIIa) blunts endotoxin induced coagulation in humans.
AUTHOR: Jilma Bernd(a); Marsik Claudia(a); Graninger Monika(a); Erhardtsen Elisabeth; Ribel Mette C; Eichler Hans-Georg(a); Geissler Klaus; Taylor Fletcher B Jr
AUTHOR ADDRESS: (a)Clinical Pharmacology, Vienna University, Vienna** Austria E-Mail: Bernd.Jilma@univie.ac.at
JOURNAL: Blood 98 (11 Part 1):p42a November 16, 2001
MEDIUM: print
CONFERENCE/MEETING: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Inhibition of the tissue factor/FVIIa pathway attenuates the activation of coagulation and prevents death in a gram-negative bacteremia primate model of **sepsis**. This **lethal** animal model suggested that tissue factor additionally influences inflammatory cascades. The current trial examined the effects of active site inhibited Factor VIIa (ASIS, FFR-rFVIIa) on endotoxin-induced procoagulant, fibrinolytic, and inflammatory responses in healthy humans. A double-blind, randomized, placebo-controlled crossover study was conducted in healthy male volunteers. Subjects received a bolus infusion of 2 ng/kg endotoxin, which was followed by a bolus infusion of ASIS (400mug/kg) or placebo 10 min later. Endotoxin injection induced inflammation, activation of coagulation, and activation and subsequent inhibition of fibrinolysis. ASIS infusion completely blocked thrombin and fibrin generation, as measured by plasma levels of prothrombin fragment (F1+2; no increase in ASIS group as compared to a 13 fold increase in the placebo group at 4 hours; $p<0.01$), soluble fibrin (TpP) and fibrin split product D-dimer. ASIS did not alter endotoxin-induced changes in the fibrinolytic system, cytokine levels, markers of endothelial (E-selectin, thrombomodulin) or platelet activation (P-selectin). In summary, ASIS effectively and selectively attenuates compensated **disseminated intravascular coagulation** in the human endotoxemia model without modifying the fibrinolytic and inflammatory response.

2265284 BIOSIS NO.: 200000018786
A selective pulmonary thrombosis associated with **sepsis**-induced **disseminated intravascular coagulation**.
AUTHOR: Aihara Masayuki(a); Nakazawa Tsugio; Dobashi Kunio; Joshita Takashi ; Kojima Masaru; Onai Masayuki; Mori Masatomo
AUTHOR ADDRESS: (a)First Department of Internal Medicine, School of Medicine, Gunma University, 3-39-15 Showa-machi, Maebashi, Gunma, 371** Japan
JOURNAL: Internal Medicine (Tokyo) 36 (2):p97-101 Feb., 1997
ISSN: 0918-2918
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: **Disseminated intravascular coagulation** (DIC) is a pathologic condition associated with critical illnesses, including **sepsis**. Recent studies have suggested that endogenous cytokines and leukocytes are involved in major roles of its pathophysiology. We report a case of **sepsis**-induced DIC due to pneumonia that was associated with diffuse and selective thrombosis in pulmonary arteries, yielding to sudden death from pulmonary massive embolism. This report suggests that the selective and **lethal** pulmonary thromboembolism progresses under the standard therapies in **sepsis**-induced DIC.

11781549 BIOSIS NO.: 199900027658
Recombinant antitrypsin Pittsburgh undergoes proteolytic cleavage during E. coli **sepsis** and fails to prevent the associated coagulopathy in a primate model.
AUTHOR: Harper P L(a); Taylor F B; Dela Cadena R A; Courtney M; Colman R W; Carrell R W
AUTHOR ADDRESS: (a)Dep. Haematol., Palmerston North Hospital, Palmerston North**New Zealand
JOURNAL: Thrombosis and Haemostasis 80 (5):p816-821 Nov., **1998**
ISSN: 0340-6245
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: During severe **sepsis** there is dramatic activation of both contact proteases and the coagulation pathway. These processes contribute to the development of shock and **disseminated intravascular coagulation** (DIC) respectively. The Pittsburgh mutant of antitrypsin (358Met-Arg) is a novel protease inhibitor with activity against both thrombin and the contact proteases and should therefore prove beneficial as a therapeutic agent in the management of septic shock. This hypothesis was supported by an earlier study in a pig model where recombinant antitrypsin Pittsburgh (rAT Pittsburgh) at a concentration of 1 muM alleviated some of the features of shock, but did not improve survival. In order to reduce the **lethal** effects of E. coli **sepsis** we postulated that a higher concentration of antitrypsin Pittsburgh would be necessary. To test this hypothesis we used rAT Pittsburgh in a primate model. This was chosen in preference to another species as E. coli **sepsis** in the primate has been well characterized and closely resembles the changes seen in man. Surprisingly this treatment did not alleviate the features of shock and unexpectedly appeared to exacerbate the associated coagulopathy. We propose two possible mechanisms for this unforeseen outcome. The first results from the broad spectrum of activity of antitrypsin Pittsburgh. As well as inhibiting thrombin and the contact proteases, the Pittsburgh mutant also inhibits activated protein C. Inhibition of the protein C system is known to exacerbate septic shock. Secondly, a significant quantity of inactive antitrypsin Pittsburgh, cleaved at the reactive centre, was detected in the plasma of the treated animals. Proteolytically altered serpins, including antitrypsin, have been shown to enhance the inflammatory process. Therefore the accumulation of cleaved rAT Pittsburgh might be expected to exacerbate septic shock.

1207710 Genuine Article#: GE810 Number of References: 141
Title: THE PATHOGENESIS OF **SEPSIS**
Author(s): BONE RC
Corporate Source: RUSH MED COLL,1753 W CONGRESS PKWY/CHICAGO//IL/60612
Journal: ANNALS OF INTERNAL MEDICINE, **1991**, V115, N6, P457-469
Language: ENGLISH Document Type: **REVIEW**
Abstract: **Sepsis** and its sequelae (**sepsis** syndrome and septic shock) are increasingly common and are still potentially **lethal** diagnoses. Many mediators of the pathogenesis of **sepsis** have recently been described. These include tumor necrosis factor-alpha (TNF-alpha), interleukins, platelet activating factor, leukotrienes, thromboxane A2, and activators of the complement cascade. Neutrophil and platelet activation may also play a role. other agents that may participate in the **sepsis** cascade include adhesion molecules, kinins, thrombin, myocardial depressant substance, beta-endorphin, and heat shock proteins. Endothelium-derived relaxing factor and endothelin-1 are released from the endothelium and seem to exert a regulatory effect, counterbalancing each other.

A central mediator of **sepsis** does not seem to exist, although TNF-alpha has been commonly proposed for this role. Animal studies are difficult to extrapolate to the clinical setting because of cross-species differences and variations in experimental design. Rather than being caused by any single pathogenic mechanism, it is more likely that **sepsis** is related to the state of activation of the target cell, the nearby presence of other mediators, and the ability of the target cell to release other mediators. Also important is the downregulation or negative feedback of these mediators or the generation of natural inflammation inhibitors, such as interleukin-4 and interleukin-8.

Endothelial damage in **sepsis** probably results from persistent and repetitive inflammatory insults. Eventually, these insults produce sufficient damage that downregulation can no longer occur; this leads to a state of metabolic anarchy in which the body can no longer control its own inflammatory response.

11991222 BIOSIS NO.: 199900271741
Lipopolysaccharide induction of tissue factor expression in rabbits.
AUTHOR: Erlich Jonathan; Fearns Colleen; Mathison John; Ulevitch Richard J; Mackman Nigel
AUTHOR ADDRESS: Scripps Research Institute, IMM-17, 10550 North Torrey Pines Rd., La Jolla, CA, 92037**USA
JOURNAL: Infection and Immunity 67 (5):p2540-2546 May, 1999
ISSN: 0019-9567
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Tissue factor (TF) is the major activator of the coagulation protease cascade and contributes to **lethality** in **sepsis**. Despite several studies analyzing TF expression in animal models of endotoxemia, there remains debate about the cell types that are induced to express TF in different tissues. In this study, we performed a detailed analysis of the induction of TF mRNA and protein expression in two rabbit models of endotoxemia to better understand the cell types that may contribute to local fibrin deposition and **disseminated intravascular coagulation**. Northern blot analysis demonstrated that lipopolysaccharide (LPS) increased TF expression in the brain, lung, and kidney. In situ hybridization showed that TF mRNA expression was increased in cells identified morphologically as epithelial cells in the lung and as astrocytes in the brain. In the kidney, in situ hybridization experiments and immunohistochemical analysis showed that TF mRNA and protein expression was increased in renal glomeruli and induced in tubular epithelium. Dual staining for TF and vWF failed to demonstrate TF expression in endothelial cells in LPS-treated animals. These results demonstrate that TF expression is induced in many different cell types in LPS-treated rabbits, which may contribute to local fibrin deposition and tissue injury during endotoxemia.